APJ acts as a dual receptor in cardiac hypertrophy.

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Public Summary:
Cardiac hypertrophy is initiated as an adaptive response to sustained overload but progresses pathologically as heart failure ensues. Here we report that genetic loss of APJ, a G-protein-coupled receptor, confers resistance to chronic pressure overload by markedly reducing myocardial hypertrophy and heart failure. In contrast, mice lacking apelin (the endogenous APJ ligand) remain sensitive, suggesting an apelin-independent function of APJ. Freshly isolated APJ-null cardiomyocytes exhibit an attenuated response to stretch, indicating that APJ is a mechanosensor. Activation of APJ by stretch increases cardiomyocyte cell size and induces molecular markers of hypertrophy. Whereas apelin stimulates APJ to activate Gαi and elicits a protective response, stretch signals in an APJ-dependent, G-protein-independent fashion to induce hypertrophy. Stretch-mediated hypertrophy is prevented by knockdown of β-arrestins or by pharmacological doses of apelin acting through Gαi. Taken together, our data indicate that APJ is a bifunctional receptor for both mechanical stretch and the endogenous peptide apelin. By sensing the balance between these stimuli, APJ occupies a pivotal point linking sustained overload to cardiomyocyte hypertrophy.

Scientific Abstract:
Cardiac hypertrophy is initiated as an adaptive response to sustained overload but progresses pathologically as heart failure ensues. Here we report that genetic loss of APJ, a G-protein-coupled receptor, confers resistance to chronic pressure overload by markedly reducing myocardial hypertrophy and heart failure. In contrast, mice lacking apelin (the endogenous APJ ligand) remain sensitive, suggesting an apelin-independent function of APJ. Freshly isolated APJ-null cardiomyocytes exhibit an attenuated response to stretch, indicating that APJ is a mechanosensor. Activation of APJ by stretch increases cardiomyocyte cell size and induces molecular markers of hypertrophy. Whereas apelin stimulates APJ to activate Galpha(i) and elicits a protective response, stretch signals in an APJ-dependent, G-protein-independent fashion to induce hypertrophy. Stretch-mediated hypertrophy is prevented by knockdown of beta-arrestins or by pharmacological doses of apelin acting through Galpha(i). Taken together, our data indicate that APJ is a bifunctional receptor for both mechanical stretch and the endogenous peptide apelin. By sensing the balance between these stimuli, APJ occupies a pivotal point linking sustained overload to cardiomyocyte hypertrophy.